doi:10.1093/brain/awq033 Brain 2010: 133; 1143–1154 | 1143

BRAIN
A JOURNAL OF NEUROLOGY

Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2

Suman Jayadev,[1] James B. Leverenz,[1,2,3] Ellen Steinbart,[1,4] Justin Stahl,[5] William Klunk,[6] Cheng-En Yu[4] and Thomas D. Bird[1,4]

1 Department of Neurology, University of Washington, Seattle, WA, USA
2 Mental Illness Research Education and Clinical Centre, Veterans Administration Puget Sound Health Care System, Seattle, WA, USA
3 Parkinson Disease Research Education and Clinical Centre, Veterans Administration Puget Sound Health Care System, Seattle, WA, USA
4 Geriatric Research Education and Clinical Centre, Seattle, WA, USA
5 Virginia Mason Clinic, Veterans Administration Puget Sound Health Care System, Seattle, WA, USA
6 Departments of Psychiatry and Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Correspondence to: Thomas D. Bird, MD,
1660 S Columbian Way,
182-GRECC, Seattle,
WA 98108, USA
E-mail: tomnroz@uw.edu

Mutations in presenilin 2 are rare causes of early onset familial Alzheimer's disease. Eighteen presenilin 2 mutations have been reported, although not all have been confirmed pathogenic. Much remains to be learned about the range of phenotypes associated with these mutations. We have analysed our unique collection of 146 affected cases in 11 Volga German families, 101 who are likely to have the same N141I mutation in presenilin 2 (54 genotyped confirmed). We have also assessed the detailed neuropathologic findings in 18 autopsies from these families and reviewed the world's literature on other presenilin 2 mutations; presenting a novel mutation that is predicted to lead to a premature truncation codon. Seven presenilin 2 mutations reported in the literature have strong evidence for pathogenicity whereas others may be benign polymorphisms. One hundred and one affected persons, with sufficient historical information from the Volga German pedigrees (N141I mutation), had a mean onset age of 53.7 years ± 7.8 (range 39–75) and mean age at death of 64.2 years ± 9.8 (range 43–88). These figures overlap with and generally fall between the results from the subjects in our centre who have late onset familial Alzheimer's disease or mutations in presenilin 1. Seizures were noted in 20 (30%) of 64 subjects with detailed medical records. Two mutation carriers lived beyond age 80 without developing dementia, representing uncommon examples of decreased penetrance. Two persons had severe amyloid angiopathy and haemorrhagic stroke. Eighteen cases had detailed histopathology available and analysed at our institution. Braak stage was five or six, amyloid angiopathy and neuritic plaques were common and more than 75% had Lewy bodies in the amygdala. TAR DNA-binding protein-43 inclusions were uncommon. In addition, a 58-year-old female with a 2 year course of cognitive decline and no family history of dementia has abnormal fludeoxyglucose-positron emission tomography imaging and a novel 2 base pair deletion in presenilin 2 at nucleotide 342/343, predicted to produce a frame-shift and premature termination. We conclude that mutations in presenilin 2 are rare with only seven being well documented in the literature. The best studied N141I mutation produces an Alzheimer's disease phenotype with a wide range of onset ages overlapping both early and late onset Alzheimer's disease, often associated with seizures, high penetrance and typical Alzheimer's disease neuropathology. A novel premature termination mutation supports loss of function or haploinsufficiency as pathogenic mechanisms in presenilin 2 associated Alzheimer's disease.

Keywords: Alzheimer's disease; presenilin 2; human genetics; dementia; amyloid; Volga German

Received December 7, 2009. Revised January 11, 2009. Accepted January 15, 2009

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer Disease; *PSEN1* = presenilin 1; *PSEN2* = presenilin 2; TDP43 = TAR DNA binding protein 43

Introduction

Four genes have been confirmed to play an important role in the pathogenesis of various forms of Alzheimer's disease. Apolipoprotein E alters the risk for, and the age at onset of, the common late onset type of Alzheimer's disease. Mutations in the amyloid precursor protein gene on chromosome 21 were first reported in 1991 and more than 30 pathogenic mutations have been described (Goate *et al*., 1991). Mutations in the presenilin 1 gene (*PSEN1*) on chromosome 14 were first reported in 1995 and more than 170 mutations have been described, making this the most common cause of autosomal dominant early onset Alzheimer's disease (Sherrington *et al*., 1995; Larner and Doran, 2006). Mutations in presenilin 2 (*PSEN2*) on chromosome 1 were first described in 1995 and only 18 potentially pathogenic mutations have subsequently been reported, making this the least common genetic cause of Alzheimer's disease (Levy-Lahad *et al*., 1995; Rogaev *et al*., 1995). The discovery of mutations in these genes has been fundamental in advancing our understanding of Alzheimer's disease. However, because mutations in *PSEN2* are rare there has never been an extensive evaluation of them or the phenotype associated with them.

The purpose of the present study is to fill this gap in our knowledge by (i) reviewing the world's literature and assessing the likelihood of pathogenicity associated with each reported *PSEN2* mutation; (ii) reporting a new frame-shift truncating mutation in *PSEN2*; and (iii) describing the clinical and pathological phenotype of the largest collection of subjects with a *PSEN2* mutation (N141I) in eleven families with the Volga German genetic founder background.

Materials and methods

We performed a PubMed search of all articles relating to mutations in *PSEN2*. These reports were analysed for number of families, number of affected generations, number of affected subjects, segregation of mutation with disease and review of the functional studies of several mutations reported by Walker *et al*. (2005).

Over the past 25 years our Alzheimer's disease Research Centre has evaluated 184 families with possible Alzheimer's disease having a 'German from Russia' ethnic background. Forty-three were Black Sea Germans from the Odessa region and 124 were Volga Germans from the Saratov region. Since the discovery of the *PSEN2* gene in 1995 we have determined that 11 of these families represent a genetic founder effect and carry the same N141I mutation in *PSEN2* (Levy-Lahad *et al*., 1995). From personal examination or medical record review we have collective detailed clinical information on 101 affected persons in these 11 families. From these evaluations we determined age of onset, age of death, likely first symptom, presence of psychotic features (delusions and/or hallucinations) and occurrence of seizures. Age at onset was defined as in our previous studies (Bird *et al*., 1988). For comparison we have also used the onset age, death age and duration data collected in our centre from 23 families with *PSEN1* mutations and 125 families each having three or more persons with late onset Alzheimer's disease.

Twelve affected subjects had formal neuropsychological testing by a variety of examiners that usually included four or more of the following tests: Wechsler Memory Scale–Revised, Wechsler Adult Intelligence Scale, Reitan Test Battery, Boston Naming, Trail Making Test, Rey Figure Drawing, Wisconsin Card Sorting, Clock Drawing, Blessed Dementia Rating Scale, California Verbal Learning Test, Category Test, Controlled Oral Word Association, Stroop and Mini Mental State Examination.

Thirty-five brain autopsies were performed in these Volga German families. Twelve were performed at outside institutions and only reports were available. Slides from 23 autopsies were available for review at our institution and 18 had sufficient material for a more detailed neuropathological examination. The additional examination included immunohistochemical assessment for tau (AT8, Endogen, 1:250), alpha-synuclein (LB509, 1:1:1000 and syn 303, 1:500; generous gifts of J. Q. Trojanowski) and TAR DNA binding proteion (TDP43; Protein Tech, 1:2000) pathology as previously described (Leverenz *et al*., 2008). For each case, we determined the Consortium to Establish a Registry for Alzheimer Disease (CERAD) neuritic plaque scores and Braak staging for neurofibrillary tangles (Braak and Braak, 1991; Mira *et al*., 1991).

Pittsburgh compound-B PET brain imaging was performed on one subject using previously described methods (Lopresti *et al*., 2005).

Results

Reported *PSEN2* mutations

Twenty-three DNA variants resulting in non-synonymous substitutions have been reported in the *PSEN2* gene (http://www.molgen.ua.ac.be/ADMutations). Four of these are known normal polymorphisms. Three variants, R29H, L143H and A252T were found in a screening of 130 individuals from seven African populations belonging to the Centre d'Etude du Polymorphisme Humain-Human Genome Diversity Panel (Guerreiro *et al*., 2008). A P334R variant has been reported in a late onset Alzheimer's disease family, though the change did not segregate with disease (Lleó *et al*., 2002*a*). Recently a R163H mutation was found in a Parkinson's disease family carrying a *de novo* alpha-synuclein A53T mutation (Puschmann *et al*., 2009). The patient carrying the gene change had cognitive deficits although her unaffected mother also carried the mutation. Eighteen have been proposed as possible disease causing mutations (Table 1 and Fig. 1). Our analysis indicates that seven of these mutations are highly likely to be pathogenic. These seven have occurred in more than one family and/or have been shown to segregate with disease in a family. In addition, Walker *et al*. (2005) found that five of these mutations produce an excessive amount of Aβ peptide in a cell culture system. Eleven other DNA variants are less likely to be pathogenic, although this remains a possibility. These 11 variants have occurred only in a single sporadic case, have not been shown to

Table 1 Reported mutations in *PSEN2*

	Number of families	Number of generations	Mean age of onset (years)	Onset age range among families (years)	Evidence for pathogenicity	Atypical or distinctive clinical features	References
A85V	1	1	66.0 ($n = 4$)	60–73	Segregates with disease. Not found in 100 healthy controls, 80 patients with sporadic Alzheimer's disease and 32 with familial dementia.	Parkinsonism, clinical diagnosis of dementia with Lewy bodies in one member	Piscopo *et al.*, 2009
T122P	2	3, 2	47.9 ($n = 4$)	45–50	Segregates with disease. Not found in 100 control chromosomes. Increases *Ab42/40* ratio.		Finckh *et al.*, 2000, 2005; Walker *et al.*, 2005
T122R	1	3	57.3 ($n = 4$)	52–65	Segregates with disease.	Frontotemporal dementia- like phenotype	Binetti *et al.*, 2003
N141I	12	4	53.7 ($n = 84$)	39–75	Segregates with disease. Increases *Ab42/40* ratio.	32% with seizures	Levy-Lahad *et al.*, 1995; Rogaev *et al.*, 1995; Finckh *et al.*, 2005; Walker *et al.*, 2005; current study
M239V	1	4	60.1 ($n = 18$)	45–83	Segregates with disease. Increases *Ab42/40* ratio.		Rogaev *et al.*, 1995; Marcon *et al.*, 2004; Walker *et al.*, 2005
M239I	1	2	50.7 ($n = 3$)	44–58	Segregates with disease. Not found in 100 control chromosomes. Increases *Ab42/40* ratio.		Finckh *et al.*, 2000; Walker *et al.*, 2005; Signorini *et al.*, 2004
T430M	1	2	55.3 ($n = 3$)	45–64	Segregates with disease. Not found in 50 healthy controls and 80 patients with Alzheimer's disease.		Lleó *et al.*, 2002*b*; Ezquerra *et al.*, 2003
R62H	1	1	62.0 ($n = 1$)	62	Not found in 118 controls in original report but was found in 20 African controls of Human Genome Diversity Panel (allele frequency 9%). Does not alter *Ab42/40* ratio.		Cruts *et al.*, 1998; Walker *et al.*, 2005; Guerreiro *et al.*, 2008
R71W	1	1	75.0 ($n = 1$)	75	Not found in 251 controls.	Microangiopathic leukoencephalopathy with white matter lacunar infarcts	Guerreiro *et al.*, 2008
S130L	2	3, 1	69.0 ($n = 3$)	65–81	Not found in 110 healthy controls and 100 patients with familial Alzheimer's disease. Does not		Tedde *et al.*, 2003; Walker *et al.*, 2005; Tomaino *et al.*, 2007;

(continued)

Table 1. Continued

	Number of families	Number of generations	Mean age of onset (years)	Onset age range among families (years)	Evidence for pathogenicity	Atypical or distinctive clinical features	References
					significantly alter *Ab42/40* ratio.		
V139M	1	2	76.0 ($n = 1$)	76	Not found in 100 healthy controls and 100 patients with familial Alzheimer's disease.		Bernardi *et al.*, 2008
V148I	1	1	71.0 ($n = 1$)	71	Not found in 95 healthy controls and 128 patients with Alzheimer's disease. Does not significantly alter *Ab42/40* ratio.		Lao, 1998; Walker *et al.*, 2005
M174V	2	1	54.0 ($n = 1$)	54	Not found in 251 controls.		Guerreiro *et al.*, 2008; Andreoli *et al.*, 2008; Clarimon *et al.*, 2008
S175Y	1	2	60.0 ($n = 1$)	60	No additional information.		Piscopo *et al.*, 2008
Q228L	1	2	60.0 ($n = 1$)	60	Not found in 100 healthy controls and 100 patients with sporadic Alzheimer's disease.		Zekanowski *et al.*, 2003
Y231C	1	2	58.5 ($n = 2$)	52–65	Not found in 100 healthy controls and 100 patients with sporadic Alzheimer's disease.	Frontotemporal dementia-like phenotype	Marcon *et al.*, 2009
V393M	1	2	50.0 ($n = 1$)	50	Not found in 384 healthy controls. Does not alter *Ab42/40* ratio.		Walker *et al.*, 2005; Lindquist *et al.*, 2008
D439A	1	2	56.0 ($n = 2$)	52–60	Not found in 6 unaffected relatives of same generation. Not found in 50 healthy controls and 80 patients with Alzheimer's disease. Does not alter *Ab42/40* ratio.		Lleó *et al.*, 2001; Walker *et al.*, 2005
K115E Fx10	1	1	56.0 ($n = 1$)	56	Mutation leads to premature truncation codon, likely to interfere with protein function.		Current study
S175C	1	2	60 ($n = 3$)	60–70	Three affected siblings with mutation.		Piscopo *et al.*, in press.

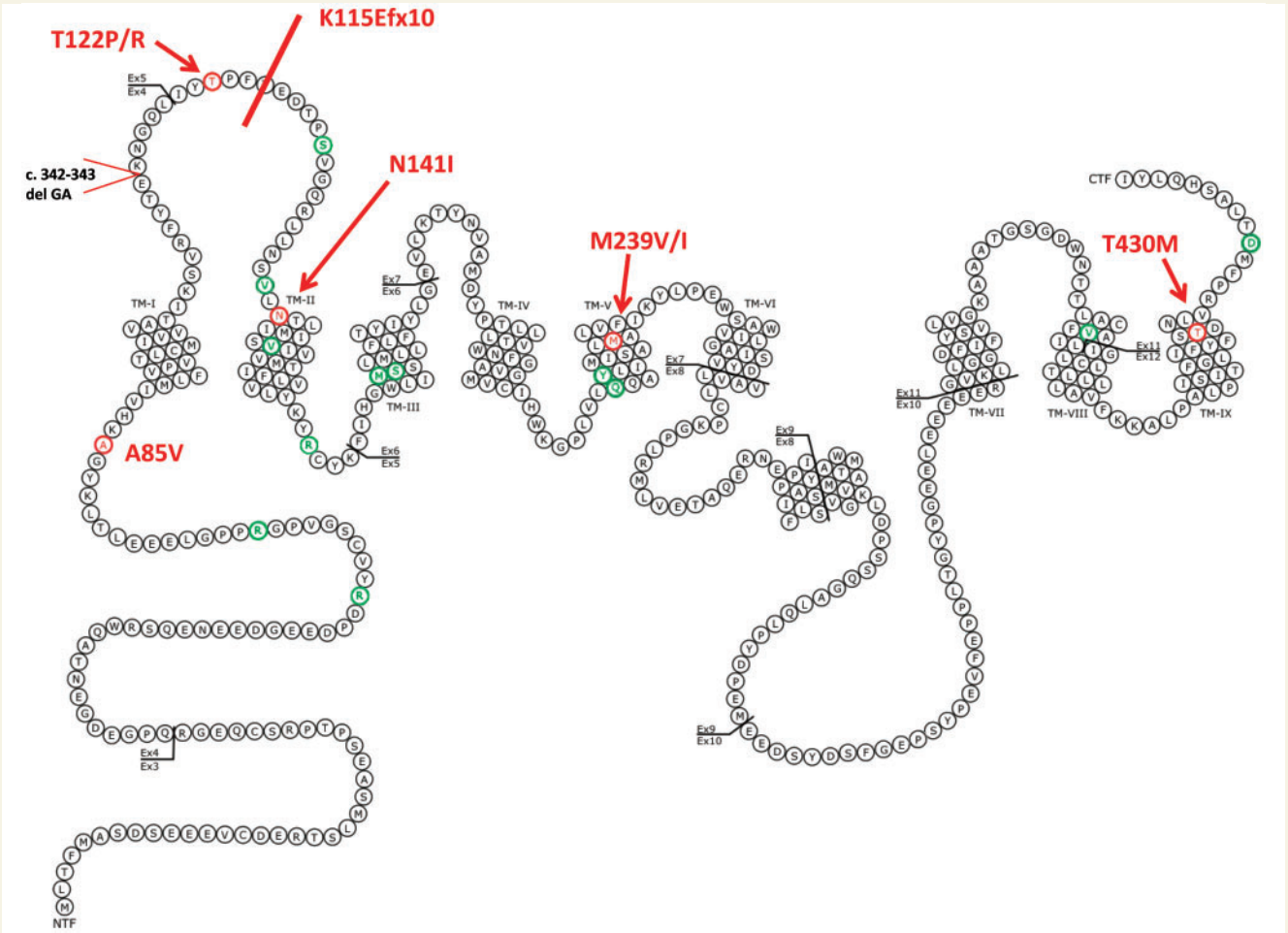

Figure 1 *PSEN2* protein showing sites of reported mutations. Probable pathogenic mutations are shown in red. Possible but uncertain mutations are shown in green. The N141I mutation is indicated with an arrow. The K115E fx10 truncation is shown at the red line and its associated mutation is indicated as c.342–343 del GA. Adapted from http://www.molgen.ua.ac.be/ADMutations (Cruts and van Broeckhoven, 1998).

segregate with disease in a family and four of them showed no abnormality in the cell culture experiments of Walker *et al*. (2005). Also, in two families having multiple affected members with late onset AD we were able to show that the R171W ''mutation'' was not segregating with the disease and is unlikely to be pathogenic.

The seven mutations that are likely to be pathogenic have occurred only in a single family in five instances, in two families with the T122P mutation and in 12 families with the N141I mutation. These seven mutations have all been associated with early onset Alzheimer's disease with a range of 39–75 years. The A85V mutation in one family was associated with somewhat later onset (60–73 years), but overlaps with the other six mutations. The S175C mutation in a newly reported family is also likely to be pathogenic (Piscopo *et al*., in press).

Figure 1 shows the location of the seven pathogenic mutations in the *PSEN2* protein.

Novel *PSEN2* deletion

A 59-year-old female has had a three year course of slowly progressive memory loss. Her family history was negative for dementia, but she knew relatively little about her extended family. Her mother died of cancer at the age of 45 and she knows nothing about her biological father. Formal neuropsychological testing revealed significant impairments in visual spatial skills and executive function. A fludeoxyglucose PET scan showed decreased uptake in the parietal and temporal lobes bilaterally. She was taking both donepezil and memantine. DNA sequencing of the amyloid precursor protein and *PSEN1* genes was normal. However, sequencing of the *PSEN2* gene (Athena Diagnostics, Inc; Worcester, MA) revealed a novel two base pair deletion of GA from nucleotide positions 342 and 343 in exon 5 leading to a frame-shift and premature termination codon in exon 6 (K115E fx10; Fig. 1).

The N141I mutation in *PSEN2*

The first mutation reported in *PSEN2* was N141I (Levy-Lahad *et al*., 1995). This mutation was identified in a collection of familial Alzheimer's disease pedigrees studied in our centre since 1983 and having the common ethnic background of being Germans from Russia. We have evaluated more than 180 such families from a

large region in Russia and the former USSR including Black Sea Germans and Volga Germans. The N141I mutation was found in 11 Volga German families all originating from three small adjacent villages southwest of Saratov, Russia (Bird *et al*., 1988).

Clinical phenotype of N141I

The clinical phenotype associated with the N141I mutation is summarized in Table 2. We have historical information on 101 affected persons in the 11 families. The number of affected people per family varies from 2 (BE family) to 17, 20 and 26 in the HD, HB and R families, respectively. Fifty-four of these affected persons have had the N141I mutation confirmed by DNA genotyping. The mean age of onset is 53.7 years with a wide range of 39 to 75 years. Mean age at death is 64.2 years with a mean disease duration of 10.6 years. Detailed medical records were available for review in 64 affected persons. The first symptom was almost always a problem with memory, thinking or orientation. The disease was slowly, relentlessly progressive and usually ended in a mute, rigid, bed ridden state. Pyramidal signs and parkinsonian features were not seen early in the disease.

We have compared this *PSEN2* phenotype with the other families ascertained in our centre with *PSEN1* mutations and those having late onset familial Alzheimer's disease (Table 3). The *PSEN1* families had an early mean age of onset of 45.5 years, but with a wide range (28–79 years). Other reported mutations in *PSEN1* have also been associated with a wide range in age of onset. The latest recorded ages of onset in *PSEN1* were 84 and 88 years in a family with the Met239Val mutation (Sherrington *et al*., 1995). The late onset Alzheimer's disease families from our centre had a mean age of onset of 71.5 years, and a very wide range (45–91 years). The Volga German *PSEN2* families have a mean onset in between these two groups (mean 53.7, range 39–75 years). Note that only three (1.4%) of the *PSEN1* cases had an onset after age 60 and these three cases all came from a single family with the A79V mutation known to be associated with a later age of onset (Brickell *et al*., 2007). The Volga German *PSEN2* families had 16 (16%) subjects with onset $\geqslant$60 years. Disease duration was shorter in the *PSEN1* cases (mean 8.4 years) whereas the duration was similar between the Volga German *PSEN2* cases (10.6 years) and the of late onset Alzheimer's disease (10.2 years).

The largest known family with a mutation in *PSEN2* is shown in Fig. 2. This is the 'R' family with 26 affected persons, an early mean onset age (49.5 years), high penetrance and a known phenocopy (see below).

Of the 64 affected persons with detailed medical records, 31% (20/64) had mention of one or more seizures. The seizures were recurrent and frequent in two subjects. Thirty-three percent (21/64) had mention of hallucinations, delusions or 'psychotic' features. Twenty-three persons were treated with a cholinesterase inhibitor and/or memantine. No systematic study of treatment effects was possible. There were only anecdotal reports of both beneficial and negative treatment results, but more than half of these families (13/23) reported some possible 'benefit'.

Formal neuropsychological testing was performed on 12 affected persons, usually 1–4 years after onset of symptoms (Supplementary Table). All individuals demonstrated memory loss with relatively spared motor function. Verbal fluency, spatial perception, calculations and executive functions were also impaired, especially as measured by the Wechsler Memory Scale–Revised and Trail Making Tests. Subjects often did well on the Boston Naming Test early in the disease.

Neuroimaging

One person in the R family (V-34) had Pittsburgh compound B imaging obtained at age 52, after about 2 years of mild symptoms. At the point this subject was imaged, Pittsburgh compound B retention was very typical of that previously reported in patients with late onset Alzheimer's disease (Klunk *et al*., 2004), with frontal, temporal and parietal/precuneus cortices and the caudate displaying especially prominent retention (Fig. 3). Since this subject was already symptomatic when scanned, it is not possible to know whether some or all pre-symptomatic *PSEN2* mutation carriers would show the striatal-predomiant pattern of Pittsburgh compound B retention reported for pre-symptomatic *PSEN1* mutation carriers (Klunk *et al*., 2007). However, in the symptomatic V-34 case, there was no indication of striatal predominance.

Penetrance and phenocopies in N141I families

Clinical penetrance of the mutation was high (>95%). Two cases of decreased penetrance by the ninth decade were noted. One subject in the HB family died at age 80 of cancer without any cognitive difficulties noticed by the family. This person had an affected mother, two affected children and he carried the N141I mutation. Another individual in the H family died at age 89 of cancer and also had no cognitive problems according to the family. This person had an affected father and three affected children with the N141I mutation. He himself had not been genotyped.

There have been three phenocopies of the common form of Alzheimer's disease in these families. One was in the R family (IV-2, Fig. 2). This individual was at risk for the disease and had the onset of a progressive dementia at age 62 years. This onset was later than the other affected persons in the R family (although within the range of the total Volga German family collection), he did not carry the N141I mutation and had an Apolipoprotein E genotype of $\varepsilon4/\varepsilon4$. Another phenocopy occurred in the W family in which an 83-year-old male had onset of mild dementia at age 79, did not have the N141I mutation (ApoE 3/3) and neuropathology showed mild to moderate signs of Alzheimer's disease. A third phenocopy was a female in the HD family with onset of progressive dementia at age 75, death at age 83 and she did not carry the *PSEN2* mutation (ApoE 3/4).

Modern German family with N141I

Nikisch *et al*. (2008) reported a small family with early onset Alzheimer's disease in modern Germany with the N141I mutation. Together we have demonstrated that this family shares the same

Table 2 Clinical phenotype of Volga German families with N141I *PSEN2* mutation

Family	Number affected*	Confirmed *PSEN2* mutation	Mean age onset ± SD (range)	Mean age death ± SD (range)	Mean duration (years) ± SD (range)	Autopsy[a]	Medical records available	First signs and symptoms	Psychosis	Seizures
BDR	5	1	40 ± 1.4 (39–41)	50.8 ± 2.3 (47–53)	9 ± 1.4 (8–10)	1	2	1 memory problems 1 personality change	1 psychosis	2
BE	2	2	61.0 ± 1.4 (60–62)	69	7	1	2	2 memory problems	na	na
E	8	3	55.0 ± 3.9 (50–60)	67.2 ± 5.9 (58–76)	10.0 ± 3.1 (6–14)	3	7	4 memory problems 4 cognitive problems 1 behavioural change 2 vision problems	na	na
H	7	5	60.3 ± 5.3 (56–68)	72.3 ± 9.3 (60–80)	16.5 ± 7.8 (11–22)	3	5	4 memory problems 2 cognitive problems	1 psychosis 1 delusions	1
HB	20	12	59.9 ± 8.3 (49–75)	72.3 ± 9.0 (58–88)	10.9 ± 3.8 (4–19)	7	13	13 memory problems	4 hallucinations 2 delusions	2
HD	17	8	52.2 ± 6.2 (45–70)	62.6 ± 7.1 (53–77)	92. ± 3.8 (3–15)	7	12	10 memory problems 4 cognitive problems	4 hallucinations 1 delusions	3
KSS	2	1	57.5 ± 3.5 (55–60)	73.0 ± 5.7 (69–77)	15.5 ± 1.5 (14–17)	1	1	1 memory problems	1 hallucinations	0
KYL	5	3	52.8 ± 14.9 (44–75)	62.8 ± 11.5 (52–78)	6.3 ± 3.5 (3–10)	2	3	3 memory problems 1 depression	1 hallucinations	1
R	26	14	49.5 ± 4.3 (40–56)	57.4 ± 7.6 (43–74)	10.3 ± 4.8 (5–23)	8	13	10 memory problems 2 cognitive problems 1 vision problem 1 personality change 1 seizures	1 hallucinations 1 delusions	8
VQT	3	1	46	70	no data	0	1	1 cognitive problems	1 hallucinations	0
W	6	4	52.0 ± 4.9 (47–58)	67.4 ± 4.9 (62–73)	14.6 ± 8.1 (5–25)	2	5	5 memory problems 2 cognitive problems	1 hallucinations 1 psychosis	3
Total 11	101	54	53.7 ± 7.8 (39–75) *n* = 85	64.2 ± 9.8 (43–88) *n* = 75	10.6 ± 4.8 (3–25) *n* = 62	35	64	53 memory problems 15 cognitive problems 3 vision problems 2 personality changes 1 behavioural change 1 depression 1 seizures	13 hallucinations 5 delusions 3 'psychosis' 21/64 (33%)	20 20/64 (31%)

na = not applicable. *Number affected: demented persons with the N141I mutation by genotyping or who had a child with the mutation.
a Autopsy: total autopsies in families of demented persons with and without genotyping.

chromosome 1q haplotype with the Volga German pedigrees and speculated that Alzheimer's original patient (Auguste D.) may have had this mutation (Yu *et al*., in press).

Neuropathology in N141I families

Eighteen brain autopsies had sufficient material available for a more detailed histopathological evaluation (Table 4). In 17 of these 18 cases, the Braak stage was five or six and the CERAD plaque score was C, fulfilling pathologic criteria for Alzheimer's disease (Braak and Braak, 1991; Mann *et al*., 1997; Mira *et al*., 1991). Alpha-synuclein staining inclusions were common in the amygdala (14/18, 78%) but much less common in the substantia nigra (7/16, 44%) and the neocortex (3/17, 18%). Only three cases (3/13, 23%) had TDP43 inclusions or neurites in the amygdala, and none had TDP43 pathology in dentate gyrus, parahippocampal gyrus or frontal cortex. Three cases (3/13, 23%) had evidence of hippocampal sclerosis.

One person in the HB family did not meet all criteria for Alzheimer's disease, having a Braak stage of only three. This individual has been reported separately (Nochlin *et al*., 1998). She had onset of a progressive dementing process similar to other family members but died due a haemorrhagic stroke; she showed severe amyloid angiopathy at autopsy. Another affected member of the H family is living at age 56 with dementia and a haemorrhagic stroke. These two cases emphasize that the amyloid angiopathy associated with this mutation can sometimes be severe.

Of the 18 autopsied cases, seven had a clinical description that included delusions, hallucinations or psychotic features. All seven had Lewy bodies in the amygdala and three had Lewy bodies in the frontal cortex (the only cases with this finding). Of the 18 autopsied cases, six had clinical evidence of seizures (two with frequent seizures). Only one of these cases had hippocampal sclerosis and it was neither of the two that had reports of recurrent seizures.

Three other families reported in the literature with a *PSEN2* mutation have had neuropathological evaluation. All had typical neuritic plaques and neurofibrillary tangles associated with classic Alzheimer's disease. A case with the M239I mutation showed that the neuritic plaques were most frequent in the amygdala

Table 3 Mean age of onset, death and duration in *PSEN1*, *PSEN2* and late onset Alzheimer's disease families

	PSEN1 (23 families)	*PSEN2* (11 families)	Late onset Alzheimer's disease (125 families)
Mean age of onset	45.5 ± 8.0 (28–79)	53.7 ± 7.8 (39–75)	71.5 ± 7.9 (45–91)
Mean age at death	54.5 ± 9.3 (37–84)	64.2 ± 9.8 (43–88)	80.8 ± 7.3 (55–103)
Mean duration	8.4 ± 3.8 (2–25)	10.6 ± 4.8 (3–25)	10.2 ± 5.1 (1–28)

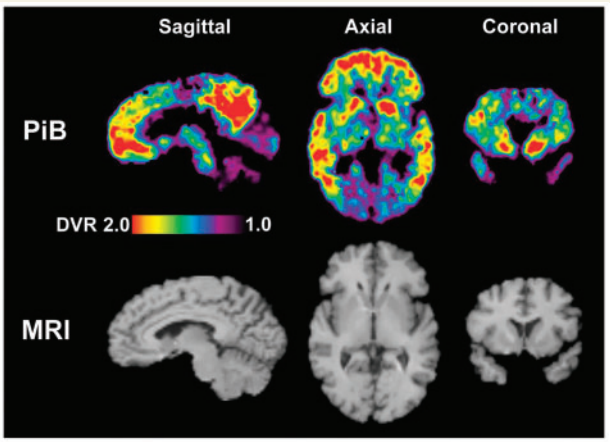

Figure 3 Pittsburgh compound B (PiB) PET and corresponding MRI images from a 52-year-old carrier of a PS2 N141I mutation from the R family with mild Alzheimer's disease (V-34). The Pittsburgh compound B PET images are parametric distribution volume ratio (DVR) images using 90 min of data and the cerebellum as reference as described in Lopresti *et al*. (2005). The MRI is a 1.5 T spoiled gradient recalled downsampled to the PET resolution. Pittsburgh compound B uptake is noted prominently in frontal and parietal cortices and caudate.

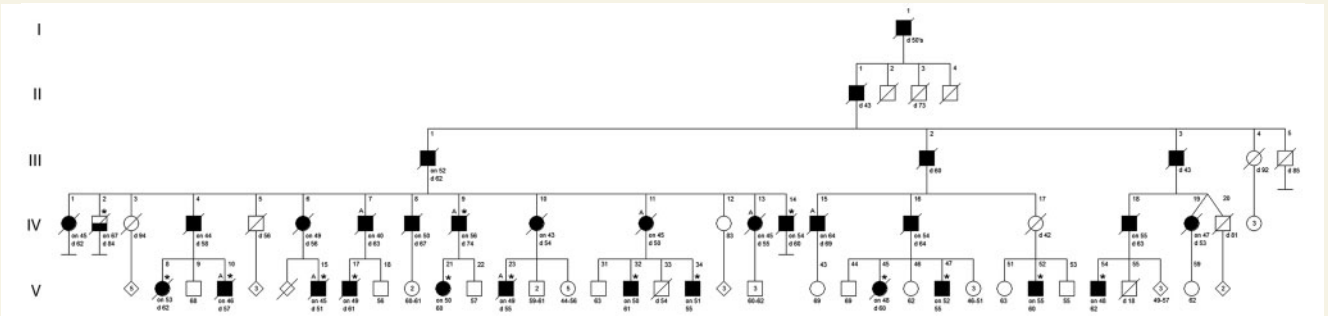

Figure 2 R family with the N141I mutation showing high penetrance with 26 known affected persons in five generations. Mean age of onset is 49.5 years and mean age at death is 57.4 years. Individual IV-2 is a phenocopy with dementia but without the *PSEN2* mutation. IV-13 and IV-15 had autopsy confirmation of Alzheimer's disease but sufficient material was not available for our detailed neuropathological study. * = persons that have been genotyped; A = autopsy; black symbols = affected Alzheimer's disease.

Table 4 Neuropathology of Volga German *PSEN2* cases

Family	Case number	Braak stage (tangles)	Plaque score	Synuclein pathology					H&E LB	TDP-43 pathology				HS
				Med	SN	Amyg	CG	FC		Amyg	DG	PHG	FC	
R	IV-9	6	C	+	+	+	+	+	–	+	–	–	–	+
	V-23	5	C	+	–	+	–	–	–	–	–	–	–	–
W	II-1	6	C	–	–	–	–	–	–	–	–	–	–	–
	III-4	6	C	–	–	+	–	–	–	–	–	–	–	–
HB	V-8	5	C	–	–	–	–	–	–	–	–	–	–	–
	V-57	3	C	–	–	+	–	–	–	–	–	–	–	+
	VI-31	5	C	–	–	+	–	–	–	–	–	–	–	+
	IV-32	6	C	–	+	+	+	na	+	na	na	na	na	na
KYL	IV-7	5	C	na	na	+	na	+	na	–	–	–	–	–
	IV-8	6	C	–	+	+	+	–	–	–	–	–	–	–
KSS	IV-30	5	C	+	+	+	+	–	–	+	–	–	–	–
E	III-21	5	C	–	+	+	+	–	–	–	–	–	–	–
BDR	V-3	5	C	–	na	–	–	–	–	–	–	–	–	–
HD	V-3	6	C	–	–	+	–	–	–	+	–	–	–	–
	IV-64	5	C	–	–	+	–	–	–	na	na	na	na	na
	IV-34	6	C	+	+	+	–	–	–	na	na	na	na	na
BE	III-7	5	C	–	–	–	–	–	–	na	na	na	na	na
H	III-11	6	C	na	+	+	na	+	–	na	na	na	na	na
Total	18	5–6 (17/18)	C	4/16	7/16	14/18	5/16	3/17	1/17	3/13	0/13	0/13	0/13	3/13

Med = medulla; SN = substantia nigra; Amyg = amygdale; CG = cingulated gyrus; FC = frontal cortex; H&E = hematoxylin and eosin; LB = Lewy bodies; DG = dentate gyrus (granule cell layer); PHG = parahippocampal gyrus; HS = hippocampal sclerosis; na = not applicable.

(Finckh *et al*., 2000). A patient with the A85V mutation had unusually abundant and widespread cortical Lewy bodies (Piscopo *et al*., 2008). Siblings with the M239V mutation had Alzheimer's disease pathology and ectopic neurons in the subcortical white matter often containing neurofibrillary tangles (Marcon *et al*., 2004). One of these patients presented with epilepsy.

Discussion

Of the three genes known to cause familial early onset Alzheimer's disease, mutations in the *PSEN2* gene are the least common. Only seven of these mutations are well documented to be pathogenic, although pathogenicity in several others remains possible. For this reason, relatively little has been reported about the phenotype associated with mutations in *PSEN2*. This study attempts to provide this knowledge. By a coincidence of genetics and history the largest body of information regarding the *PSEN2* phenotype comes from the Volga German families, which represent a founder effect for the N141I mutation.

It is unclear why mutations in *PSEN2* are rarely identified. One possibility is that they are less likely to be recognized because of the relatively later age of onset in many cases. It is likely that with the advent of more readily available and less expensive genetic testing, the number of families identified with mutations in *PSEN2* will increase. This is especially likely to be the case when more patients with onset of Alzheimer's disease in the sixth and seventh decades are studied. Furthermore, defects in *PSEN2* function may be covered by the normal function of its close homolog *PSEN1*. This phenomenon has been well illustrated in transgenic mice experiments. Mice with a knockout of *PSEN2* are viable, but knockout of both *PSEN2* and *PSEN1* is lethal (Herreman *et al*., 1999). However, despite the overlap between presenilin 1 and presenilin 2, *in vitro* studies support unique roles of presenilin 2 in mammalian physiology. The two presenilins are under different transcriptional control during development and presenilin 2 has been shown to mediate cell signalling pathways not shared with presenilin 1 (Lee *et al*., 1996; Kang *et al*., 2006).

The novel mutation in *PSEN2* (K115Efx10) reported in this study is important because, unlike all other reported *PSEN2* mutations, it results in a frame-shift and a premature termination codon. A splice-site mutation leading to a frame-shift and premature termination codon has been reported in *PSEN1* and hypothesized by the author to lead to haploinsufficiency (Tysoe *et al*., 1998). What remains to be determined is whether this shortened transcript is transcribed to yield a markedly truncated protein or, more likely, if it is instead subject to nonsense mediated decay (Holbrook *et al*., 2004). If indeed this mutation leads to a degraded transcript and haploinsufficiency, then such mutations in *PSEN2* and *PSEN1* could cause disease by a loss of function, similar to what has been described for progranulin gene mutations in patients with frontotemporal dementia (Baker *et al*., 2006; Yagi *et al*., 2008). *PSEN1* and *PSEN2* are part of the amyloid precursor protein gamma secretase complex and there is evidence that mutations in these proteins decrease the production of Aβ40 relative to Aβ42 and result in a greater proportion of the more toxic Aβ42 (De Strooper *et al*., 2007; Fluhrer *et al*., 2008).

The age of onset associated with mutations in *PSEN2* is typically in the sixth decade (50s) but with a wide range from 39 to 75 years. This range overlaps with the generally earlier onset associated with *PSEN1* mutations and the later onset seen in the more common form of Alzheimer's disease. The reasons underlying the

somewhat later mean age of onset and broader range in onset ages compared with mutations in *PSEN1* remain unclear. Again, this could reflect partial replacement of *PSEN2* function by normal *PSEN1*. Also, *APOE* genotype has been shown to influence age of onset in both *PSEN1* and *PSEN2* (Pastor *et al.*, 2003; Wijsman *et al*., 2005). Marchani and colleagues (in press) have identified three additional genetic loci modifying age at onset in the Volga German *PSEN2* families (1q23, 7q33 and 17p13). However, once the disease process has begun there is great overlap in duration of the clinical phenotype between the two genes, although the earliest onset *PSEN1* cases tend to have a more rapid decline. Early and progressive defects in memory and executive functions are common with relative sparing of naming function in persons with *PSEN2* mutations.

The occurrence of seizures in 31% of the Volga German cases is surprisingly high. The frequency of seizures occurring in common late onset Alzheimer's disease is difficult to determine but has been reported to be 1.5–20% (Scarmeas *et al*., 2009). It is acknowledged that these numbers are imprecise because patients with Alzheimer's disease are rarely observed carefully in the end stages of the disease (Risse *et al*., 1990). A higher frequency of seizures has also been reported with mutations in *PSEN1*, and certain mutations in that gene appear to have an especially high frequency of seizures (Larner and Doran, 2006; Palop and Mucke, 2009). Transgenic mice expressing the N141I mutation have been shown to have altered seizure thresholds in response to kainate, although results have varied, probably related to technical differences (Schneider *et al*., 2001; Schulte *et al*., 2009). The exact cause of the relatively frequent seizures is uncertain, but could relate to Aβ amyloid toxicity, cytoskeletal dysfunction associated with abnormal tau, cerebral vascular pathology, neurotransmitter dysfunction or a combination of these factors (Cook *et al*., 2005; Larner, 2009; Yand *et al*., 2004). We did not observe an association of hippocampal sclerosis with seizures in our cases.

Penetrance is very high (>95%) with mutations in *PSEN2* just as with mutations in *PSEN1*. Occasional phenocopies are expected because of the common occurrence of the more general form of late onset Alzheimer's disease. These factors play a role in the genetic counselling and genetic testing of these families. The relatively small experience with genetic testing in early onset Alzheimer's disease families has been similar to that with Huntington's disease (Steinbart *et al*., 2001).

Overall, neuropathological changes associated with *PSEN2* mutations are those of typical Alzheimer's disease with extensive neuritic plaque formation and neurofibrillary tangle accumulation. Of note is that amyloid angiopathy may be prominent and even produce haemorrhagic stroke (Nochlin *et al*., 1998). Consistent with previous reports in both sporadic and familial Alzheimer's disease we also found very frequent alpha synuclein pathology in the amygdala (Leverenz *et al*., 2006, 2008; Tsuang *et al*., 2006). Neocortical alpha synuclein pathology was uncommon, but appeared to be associated with hallucinations and delusions. TDP43 pathologic change was uncommon in our cases, as has been reported in sporadic Alzheimer's disease (Amador-Ortiz *et al*., 2007). Because of recent reports of Pittsburgh compound B binding in the striatum in cases with *PSEN1* mutations we are in the process of evaluating this region in the *PSEN2* subjects (Klunk *et al*., 2007).

This study has several weaknesses. Many of the family members were evaluated at different times, by different examiners, in different locations and using different techniques. Thus, records were often incomplete or mismatched. Detailed, systematic studies of clinical and neuropathological phenotypes could only be done on a representative selection of cases. Nevertheless, this remains the largest and most detailed study of families with mutations in *PSEN2* and forms a solid basis for future investigations of this important type of Alzheimer's disease.

Acknowledgements

The VQT family was ascertained by Dr J. Cummings. S. Watson assisted with analysis of the neuropsychological testing.

Funding

Department of Veterans Affairs, National Institute on Aging/NIH (Grants Nos AG005136-24, P50 AG005133, R37 AG025516 and P01 AG025204).

Conflict of interest: GE Healthcare holds a license agreement with the University of Pittsburgh based on the PiB technology described in this manuscript. Dr Klunk is a co-inventor of PiB and, as such, has a financial interest in this license agreement. GE Healthcare provided no grant support for this study and had no role in the design or interpretation of results or preparation of this manuscript. All other authors have no conflicts of interest with this work and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Bird is on the Speakers Bureau of and receives licensing fees from Athena Diagnostics, Inc.

Supplementary material

Supplementary material is available at *Brain* online.

References

Amador-Ortiz C, Lin W-L, Ahmed Z, Personett D, Davies P, Duara R, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann Neurol 2007; 61: 435–45.

Andreoli V, Trecroci F, La Russa A, Di Palma G, Quattrone A, Cittadella R. Gene symbol: *PSEN2*. Disease: Alzheimer disease. Hum Genet 2008; 124: 304.

Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006; 442: 916–9.

Bernardi L, Tomaino C, Anfossi M, Gallo M, Geracitano S, Puccio G. Late onset familial Alzheimer's disease: novel presenilin 2 mutation and PS1 E318G polymorphism. J Neurol 2008; 255: 604–6.

Binetti G, Signorini S, Squitti R, Alberici A, Benussi L, Cassetta E, et al. Atypical dementia associated with a novel presenilin-2 mutation. Ann Neurol 2003; 54: 832–6.

Bird TD, Lampe TH, Nemens EJ, Miner GW, Sumi SM, Schellenberg GD. Familial Alzheimer's disease in American decendents of the Volga Germans: probable genetic founder effect. Ann Neurol 1988; 23: 25–31.

Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol Berl 1991; 82: 239–259.

Brickell KL, Leverenz JB, Steinbart EJ, Rumbaugh M, Schellenberg GD, Nochlin D, et al. Clinicopathological concordance and discordance in three monozygotic twin pairs with familial Alzheimer's disease. J Neurol Neurosurg Psych 2007; 78: 1050–5.

Clarimon J, Guerreiro R, Lleó A, Guardia C, Blesa R, Gomez-Isla T, et al. Genetic screening in a large cohort of early-onset alzheimer's disease patients from Spain: novel mutations in the amyloid precursor protein and presenilins. International Congress of Alzheimer Disease P3–213. Alzheimer Association, Chicago, IL, 2008. p. T583.

Cook DG, Li X, Cherry SD, Cantrell AR. Presenilin 1 deficiency alters the activity of voltage-gated Ca2+ channels in cultured cortical neurons. J Neurophysiol 2005; 94: 4421–9.

Cruts M, van Broeckhoven C. Presenilin mutations in Alzheimer's disease. Human Mutation 1998; 11: 183–90.

Cruts M, van Duijn CM, Backhovens H, van den Broeck M, Wehnert A, Serneels S, et al. Estimation of the genetic contribution of presenilin-1 and -2 mutations in a population-based study of presenile Alzheimer disease. Hum Mol Genet 1998; 7: 43–51.

De Strooper B. Loss of fuction presenilin mutations in Alzheimer disease: talking point on the role of presenilin mutations in Alzheimer disease. EMBO Rep 2007; 8: 141–6.

Ezquerra M, Lleó A, Castellvi M, Queralt R, Santacruz P, Pastor P, et al. A novel mutation in the *PSEN2* gene (T430M) associated with variable expression in a family with early-onset Alzheimer disease. Arch Neurol 2003; 60: 1149–51.

Finckh U, Alberici A, Antoniazzi M, Benussi L, Fedi V, Giannini C, et al. Variable expression of familial Alzheimer disease associated with Presenilin 2 mutation M239I. Neurology 2000; 54: 2006–8.

Finckh U, Kuschel C, Anagnostouli M, Patsouris E, Pantes GV, Gatzonis S, et al. Novel mutations and repeated findings of mutations in familial Alzheimer disease. Neurogenetics 2005; 6: 85–9.

Fluhrer R, Fukumori A, Martin L, Grammer G, Haug-Kroper M, Klier B, et al. Intramembrane proteolysis of GXGD-type aspartyl proteases is slowed by a familial Alzheimer disease-like mutation. J Bio Chem 2008; 283: 30121–8.

Goate A, Chartier-Harlin M-C, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 1991; 349: 704–6.

Guerreiro RJ, Baquero M, Blesa R, Boada M, Bras JM, Bullido MJ, et al. Genetic screening of Alzheimer's disease genes in Iberian and African samples yields novel mutations in presenilins and APP. Neurobio Aging 2008. Epub ahead of print; PMID: 18667258.

Herreman A, Hartmann D, Annaert W, Saftig P, Craessaerts K, Serneels L, et al. Presenilin 2 deficiency causes a mild pulmonary phenotype and no changes in amyloid precursor protein processing but enhances the embryonic lethal phenotype of presenilin 1 deficiency. PNAS 1999; 96: 11872–7.

Holbrook JA, Neu-Yilik G, Hentze MW, Kulozik AE. Nonsense-mediated decay approaches the clinic. Nat Genet 2004; 36: 801–8.

Kang DE, Yoon IS, Repetto E, Busse T, Yermian N, Ie L, et al. Presenilins mediate phosphatidylinositol 3-kinase/AKT and ERK activation via select signaling receptors. Selectivity of PS2 in platelet-derived growth factor signaling. J Biol Chem 2006; 280: 31537–47.

Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. Ann Neurol 2004; 55: 306–19.

Klunk WE, Price JC, Mathis CA, Tsopelas ND, Lopresti BJ, Ziolko SK, et al. Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees. J Neurosci 2007; 27: 6174–84.

Lao JI, Beyer K, Fernandez-Novoa L, Cacabelos R. A novel mutation in the predicted TM2 domain of the presenilin 2 gene in a Spanish patient with late-onset Alzheimer's disease. Neurogenetics 1998; 1: 293–6.

Larner AJ. Epileptic seizures in AD patients. Neuromol Med 2009 Jun 26. Epub ahead of print; PMID: 19557550.

Larner AJ, Doran M. Clinical phenotypic heterogeneity of Alzheimer's disease associated with mutations of the presenilin-1 gene. J Neurol 2006; 253: 139–58.

Lee MK, Slunt HH, Martin LJ, Thinakaran G, Kim G, Gandy SE, et al. Expression of presenilin 1 and 2 (PS1 and PS2) in human and murine tissues. J Neurosci 1996; 16: 7513–25.

Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, et al. Candidate gene for the chromosome 1 familial Alzheimer' disease locus. Science 1995; 269: 973–7.

Lindquist SG, Hasholt L, Bahl JM, Heegaard NH, Andersen BB, Nørremølle A, et al. A novel presenilin 2 mutation (V393M) in early-onset dementia with profound language impairment. Eur J Neurol 2008; 15: 1135–9.

Lleó A, Castellví M, Blesa R, Oliva R. Uncommon polymorphism in the presenilin genes in human familial Alzheimer's disease: not to be mistaken with a pathogenic mutation. Neurosci Lett 2002a; 318: 166–8.

Lleó A, Blesa R, Gendre J, Castellvi M, Pastor P, Queralt R, et al. A novel presenilin 2 gene mutation (D439A) in a patient with early-onset Alzheimer's disease. Neurology 2001; 57: 1926–8.

Lleó A, Blesa R, Queralt R, Ezquerra M, Molinuevo JL, Peña-Casanova J, et al. Frequency of mutations in the presenilin and amyloid precursor protein genes in early-onset Alzheimer disease in Spain. Arch Neurol 2002b; 59: 1759–63.

Lopresti BJ, Klunk WE, Mathis CA, Hoge JA, Ziolko SK, Lu X, et al. Simplified quantigication of Pittsburgh compound B amyloid imaging PET studies: a comparative analysis. N Nucl Med 2005; 46: 1956–72.

Leverenz JB, Fishel MA, Peskind ER, Montine TJ, Nochlin D, Steinbart EJ, et al. Lewy body pathology in familial Alzheimer disease: evidence for disease- and mutation-specific pathologic phenotype. Arch Neurol 2006; 63: 370–6.

Leverenz JB, Hamilton R, Tsuang DW, Schantz A, Vavrek D, Larson EB, et al. Empiric refinement of the pathologic assessment of Lewy-related pathology in the dementia patient. Brain Pathol 2008; 18: 220–4.

Mann DMA, Iwatsubo T, Nochlin D, Sumi SM, Levy-Lahad E, Bird TD. Amyloid (Aβ) deposition in chromosome 1-linked Alzheimer's disease: the Volga German families. Ann Neurol 1997; 41: 52–7.

Marchani EE, Bird TD, Steinbart EJ, Rosenthal E, Yu CE, Schellenberg GD, et al. Evidence for three loci modifying age-at-onset of Alzheimer's disease in early-onset *PSEN2* families. Neuropsych Genet, in press.

Marcon G, di Fede G, Giaccone G, Rossi G, Giovagnoli AR, Maccagnano E, et al. A novel Italian presenilin 2 gene mutation with prevalent behavioral phenotype. J Alzheimers Dis 2009; 16: 509–11.

Marcon G, Gianccone G, Cupidi C, Balestrieri M, Beltrami CA, Finato N, et al. Neuropathologic and clinical phenotype of an Italian Alzheimer family with M239V mutation of presenilin 2 gene. J Neuropath Ex Neurol 2004; 63: 199–209.

Mira SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991; 41: 479–86.

Nikisch G, Hertel A, Keißling B, Wagner T, Krasz D, Hofmann E, et al. Three-year follow-up of a patient with early-onset Alzheimer's disease with presenilin-2 N141I mutation case report and review of the literature. Eur J Med Res 2008; 13: 579–84.

Nochlin D, Bird TD, Nemens EJ, Ball JJ, Sumi SM. Amyloid angiopathy in a Volga German family with Alzheimer's disease and a presenilin 2 (N141I) mutation. Annals of Neurology, 1998; 43: 131–5.

Palop JL, Mucke L. Epilepsy and cognitive impairments in Alzheimer disease. Arch Neurol 2009; 66: 435–40.

Pastor P, Roe CM, Villegas A, Bedoya G, Chakraverty S, Garcia G, et al. Apolipoprotein E4 modifies Alzheimer's disease onset in an E280A PS1 kindred. Ann Neurol 2003; 54: 163–9.

Piscopo P, Marcon G, Piras MR, Crestini A, Malvezzi Campeggi L, Deiana E, et al. A novel *PSEN2* mutation associated with a peculiar phenotype. Neurology 2009; 70: 1549–54.

Piscopo P, Talarico G, Spadoni O, Malvezzi-Campeggi L, Crestini A, Gasparini M, et al. A novel Italian Presenilin 2 mutation (S175Y). International Congress of Alzheimer Disease P3–251. Alzheimer Association, Chicago, IL, 2008. p. T595.

Piscopo P, Talarico G, Crestini A, Gasparini M, Malvezzi-Cameggi L, Piacentini E, et al. A Novel Mutation in the Predicted TM3 Domain of the PSEN2 Gene in an Italian Pedigree with Atypical Alzheimer's Disease. J Alz Dis (in press).

Puschmann A, Ross OA, Vilariño-Güell C, Lincoln SJ, Kachergus JM, Cobb SA, et al. A Swedish family with de novo alpha-synuclein A53T mutation: evidence for early cortical dysfunction. Parkinsonism Relat Disord 2009; 15: 627–32.

Risse SC, Lampe TH, Bird TD, Nochlin D, Sumi SM, Keenan T, et al. Myoclonus, seizures, and paratonia in Alzheimer disease. Alzheimer Dis Assoc Disord 1990; 4: 217–25.

Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, et al. Familial Alzheimer's disease in Kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease Type 3 gene. Nature 1995; 376: 775–8.

Scarmeas N, Honig LS, Choi H, Cantero J, Brandt J, Blacker D, et al. Seizures in Alzheimer disease: who, when, and how common? Arch Neurol 2009; 66: 992–7.

Schneider I, Reverse D, Dewachter I, Ris L, Caluwaerts N, Kuiperi C, et al. Mutant presenilins disturb neuronal calcium homeostasis in the Brain of transgenic mice, decreasing the threshold for excitotoxicity and facilitating long-term potentiation. J Bio Chem 2001; 276: 11539–44.

Schulte EC, Slawik H, Schule R, Gunther T, Hull M. Alterations in excitotoxicity and prostagandin metabolism in a transgenic mouse model of Alzheimer's disease. Neurochem Int 2009; 55: 689–96.

Sherrington R, Rogaev EI, Liang Y, Rogaev EA, Levesque G, Ikeda M, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995; 375: 754–60.

Signorini S, Ghidoni R, Barbiero L, Benussi L, Binetti G. Prevalence of pathogenic mutations in an Italian clinical series of patients with familial dementia. Curr Alz Res 2004; 1: 215–8.

Steinbart E, Smith C, Poorkaj P, Bird T. The impact of DNA testing for early onset familial Alzheimer's disease and frontotemporal dementia. Arch Neurol 2001; 58: 1828–31.

Tedde A, Nacmias B, Ciantelli M, Forleo P, Cellini E, Bagnoli S, et al. Identification of new presenilin gene mutations in early-onset family Alzheimer disease. Arch Neurol 2003; 60: 1541–4.

Tomaino C, Bernardi L, Anfossi M, Costanzo A, Ferrise F, Gallo M, et al. Presenilin 2 Ser130Leu mutation in a case of late-onset "sporadic" Alzheimer's disease. J Neurol 2007; 254: 391–3.

Tsuang DW, Rieske RG, Purganan KM, David AC, Montine TJ, Schellenberg GD, et al. Lewy body pathology in late-onset familial Alzheimer's disease: a clinicopathological case series. J Alz Dis 2006; 9: 235–242.

Tysoe C, Whittaker J, Xuereb J, Cairns NJ, Cruts M, van Broeckhoven C, et al. A presenilin-1 truncating mutation is present in two cases with autopsy-confirmed early-onset Alzheimer disease. Am J Hum Genet 1998; 62: 70–6.

Walker ES, Martinez M, Brunkan AL, Goate A. Presenilin 2 familial Alzheimer's disease mutations result in partial loss of function and dramatic changes in Aβ 42/40 ratios. J Neurochem 2005; 92: 294–301.

Wijsman EM, Daw EW, Yu X, Steinbart EJ, Nochlin D, Bird TD, et al. APOE and other loci affect age-at-onset in Alzheimer's disease families with PS2 mutation. AM J Med Gene B 2005; 132B: 14–20.

Yagi T, Giallourakis C, Mohanty S, Scheidig C, Shen J, Zheng H, et al. Defective signal transduction in B lymphocytes lacking presenilin proteins. Proc Natl Acad Sci USA 2008; 105: 979–984.

Yang Y, Kinney GA, Spain WJ, Breitner JCS, Cook DG. Presenilin-1 and intracellular calcium stores regulate neuronal glutamate uptake. J Neurochem 2004; 88: 1361–72.

Yu CE, Marchani E, Nikisch G, Muller U, Nolte D, Hertel A, et al. The N141I mutation in presenilin-2: implications for the quintessential case of Alzheimer disease. Arch Neurol, in press.

Zekanowski C, Styczynska M, Peplonska B, Gabryelewicz T, Religa D, Ilkowski J, et al. Mutations in presenilin 1, presenilin 2, and amyloid precursor protein genes in patients with early-onset Alzheimer's disease in Poland. Exp Neurol 2003; 184: 991–6.